

**Amendments to the Claims:**

This listing of claims will replace all prior versions, and listings, of claims in the application.

**Listing of Claims:**

1. (currently amended) A method of detecting whether a candidate prion polypeptide (PrP) including a target epitope recognized by an antibody designated as 3F4 and/or an antibody designated as 6H4 is in i) a wildtype conformation or ii) an aggregated or misfolded conformation in a sample, comprising:

contacting the prion polypeptide with a peroxynitritechemical-modifying agent that chemically reacts with and selectively blocks an accessible target epitope, wherein in the wildtype conformation, the target epitope is accessible and reacts with the blocking-agentperoxynitrite, and wherein in the aggregated or misfolded conformation, the target epitope is inaccessible and the target epitope cannot react with the peroxynitriteblocking-agent;

removing the unreacted peroxynitritechemical-modifying agent from contact with the prion polypeptide;

disaggregating or denaturing the candidate prion polypeptide to convert any inaccessible target epitope to accessible target epitope,

contacting the prion polypeptide with an aptamer-antibody that binds selectively to the target epitope that was converted from inaccessible target epitope to accessible target epitope, wherein binding between the aptamer-antibody and converted target epitope indicates that the prion candidate polypeptide was in an aggregated or misfolded conformation and wherein lack of binding between the aptamer-antibody and the target epitope indicates that the prion polypeptide was in a wildtype conformation in the sample.

2. (currently amended) The method of claim 1, wherein the candidate polypeptide comprises prion protein; the wild type conformation comprises the conformation of wild type prion protein and the aggregated or misfolded conformation comprises the conformation of PrP<sup>Sc</sup>.

3-10. (cancelled)

11. (previously presented) The method of claim 1, wherein the polypeptide is denatured by heat and/or detergent and/or chaotropic agents.

12. (previously presented) The method of claim 1, wherein the polypeptide is disaggregated by treatment with a disaggregation agent to disaggregate the polypeptide from the aggregated polypeptides.

13. (original) The method of claim 12, wherein the disaggregation agent is selected from at least one of the group consisting of chaotropic agents, detergent and heat.

14. (original) The method of claim 13, wherein the detergent comprises SDS.

15-16. (cancelled)

17. (previously presented) The method of claim 16, wherein the antibody comprises the antibody designated as 6H4 or the antibody designated as 3F4.

18-19. (cancelled)

20. (currently amended) The method of claim 1, wherein the presence of the aggregated conformation is indicative of a disease caused by protein aggregation.

21. (currently amended) The method of claim 20, wherein the disease comprises a prion disease.

22. (currently amended) The method of claim 20, wherein the prion disease comprises BSE or CJD.

23-29. (cancelled)

30. (previously presented) The method of claim 1, wherein the polypeptide is in a postmortem or antemortem sample selected from the group consisting of CSF, serum, blood, urine, biopsy sample and brain tissue.

31-38. (cancelled)

39. (currently amended) A method of detecting whether a candidateprion polypeptide that has been contacted with peroxynitritechemical-modifying-agent is in i) a wildtype conformation or ii) an aggregated or misfolded conformation, wherein the prion candidatepolypeptide comprises at least one target epitope recognized by an antibody designated as 3F4 and/or an antibody designated as 6H4 and, following contact with the peroxynitritechemical-modifying-agent and removal of the peroxynitritechemical-modifying-agent, the prioncandidate-polypeptide has been disaggregated or denatured to convert any inaccessible target epitope to an accessible target epitope, the method comprising:

contacting the prion polypeptide with an aptamer-or antibody that binds selectively to the target epitope that was converted from inaccessible target epitope-to-accessible-target epitope, wherein binding between the aptamer-or antibody and the converted target epitope indicates that the prioncandidate polypeptide was in an aggregated or misfolded conformation and wherein lack of binding between the aptamer-or antibody and the target epitope indicates that the polypeptide was in a wild type conformation.

40. (cancelled)

41. (currently amended) The method of claim 1, wherein binding between the aptamer or antibody and the converted target epitope is detected using dissociation enhanced lanthanide fluoroimmunoassay and time-resolved fluorescence.

42-46. (cancelled)

47. (currently amended) The method of claim 1, wherein the target epitope is inaccessible because the prioncandidate-polypeptide is aggregated.

48. (currently amended) The method of claim 1, wherein the target epitope is inaccessible because the prioncandidate-polypeptide is misfolded.

49. (currently amended) A method of detecting whether a candidateprion polypeptide including a target epitope is in i) a wildtype conformation or ii) an aggregated or misfolded conformation, comprising:

contacting the prion polypeptide with a-chemical-modifying agent~~peroxynitrite~~ that chemically reacts with and selectively blocks to block an accessible target epitope, wherein the target epitope is recognized by an antibody designated as 3F4 and/or an antibody designated as 6H4, and wherein in the aggregated or misfolded conformation, the target epitope is accessible and reacts with the peroxynitritechemical-modifying-agent, and wherein in the wildtype conformation, the target epitope is inaccessible and the target epitope cannot react with the peroxynitritechemical-modifying-agent;

removing unreacted peroxynitritechemical-modifying agent from contact with the prion polypeptide;

disaggregating or denaturing the prioncandidate polypeptide to convert any inaccessible target epitope to accessible target epitope; and

contacting the prion polypeptide with an aptamer—or antibody that binds selectively to the target epitope—that was converted from inaccessible target epitope—to-accessible-target epitope, wherein binding between the aptamer—or antibody and the converted target epitope indicates that the prioncandidate polypeptide was in a wildtype conformation and wherein lack of binding between the aptamer—or—antibody and the target epitope indicates that the prion polypeptide was in an aggregated or misfolded conformation.

50. (cancelled)

51. (currently amended) The method of claim 1, wherein prior to contacting the peroxynitritechemical modifying agent with the prioncandidate polypeptide, the prioncandidate polypeptide is pretreated by one or more of the following methods: adsorption, precipitation, or centrifugation.

52. (currently amended) The method of claim 39.1 wherein the chemical modifying agent chemically reacts with and selectively blocks the target epitope recognized by the antibody comprises the antibody designated as 3F4 or the target epitope recognized by the antibody designated as 6H4.

53. (cancelled)

54. (previously presented) The method of claim 11 where the chaotropic agent is selected from guanidine salts, urea or thiourea.

55. (previously presented) The method of claim 13 wherein the chaotropic agent is selected from guanidine salts, urea or thiourea.

56. (currently amended) A method of detecting whether a sample contains prion polypeptide (PrP) in a i) wildtype or ii) aggregated conformation, comprising:

contacting polypeptide in the sample with peroxynitrite to block accessible target epitope on the PrP, wherein the target epitope is recognized by an antibody designated as 3F4 and/or an antibody designated as 6H4 and wherein in the wildtype conformation, the target epitope is accessible and reacts with the peroxynitrite, and wherein in the aggregated conformation, the target epitope is inaccessible and the target epitope cannot react with the peroxynitrite;

removing unreacted peroxynitrite from contact with the PrP;

disaggregating or denaturing the PrP to convert any inaccessible target epitope to accessible target epitope; and

contacting the sample with ansaid antibody that binds selectively to the target epitope, that was converted from inaccessible target epitope to accessible target epitope, wherein binding between the antibody and the converted target epitope indicates that the PrP was in an aggregated conformation and wherein lack of binding there-between indicates that the PrP was in a wildtype conformation.